December 5, 2003

Dr. Leslie Scott
U.S. Environmental Protection Agency
Risk Assessment Division
Mail Stop 7403M
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

RE: Company Identification number
Aldicarb oxime CAS N0 1646-75-9

Dear Dr. Scott:

On November 22, 1999, Honeywell (then AlliedSignal) sent a letter to Ms. Carol Browner with commitments to conduct evaluations on three of our HPV chemicals. Included in this letter was Aldicarb Oxime (ADO; 2-methyl-2-methylthiopropanal oxime). At that time we anticipated completing the initial assessment in 2002. However, due to the time required for other HPV chemicals, the initial assessment was not completed until 2003. I am pleased to submit the SIDS dossier on ADO to EPA at this time.

As you will note there is information for most SIDS data points. Given the limited market, one customer at one site and our controlled product, again one plant at one site, we have considered the available data to be adequate for a risk assessment. However, we do realize that existing data does not fill all SIDS endpoints especially in the developmental toxicity area. We do request that during EPA's review of this submission, consideration be given to the low levels of exposure and the controlled production and consumption of this substance.

Should there be any questions regarding the submission of this dossier please call me at 973-455-3672 or send me an e-mail at george.rusch@honeywell.com. If you are not the correct recipient for this dossier, I would appreciate your sending to the correct person on behalf of Honeywell as I will be away chairing an AEGL committee meeting. We look forward to working with EPA to complete this review.

Sincerely,

George M. Rusch, Ph.D., DABT, FATS
Director of Toxicology and Risk Assessment

201-15512

2-METHYL-2-METHYLTHIOPROPANAL OXIME

(ALDICARB OXIME)

CAS Number 1646-75-9

USEPA HPV CHALLENGE PROGRAM SUBMISSION

Submitted by:

Honeywell International Inc.
101 Columbia Road
Morristown, NJ 07962

Date: Dec. 5, 2003

Prepared by:

Industrial Health Foundation
34 Penn Circle West
Pittsburgh PA 15206-3612

CONTENTS

SUBMISSION OVERVIEW AND TESTING PLAN FOR 2-METHYL-2-METHYLTHIOPROPANAL OXIME (ADO)

Aldicarb oxime (ADO) is used as an agricultural intermediate in the production of carbamate pesticides. It is produced by Honeywell International Inc. at its plant in Hopewell Virginia. It is sold to one customer who uses it at only one one site, where ADO is reacted with methyl isocyanate to produce an aldicarb formulation (Aldicarb, Temik). This reaction is believed to occur in a sealed system to prevent exposure to the methyl isocyanate.

ADO is primarily used by industrial workers experienced in the handling of substances of greater toxicity. Significant airborne levels of ADO should not occur due to its low vapor pressure. Honeywell has established PEL of 10 ppm (54.3 mg/$m^{3)}$ as an 8 hour TWA.

ADO is a clear, colorless liquid sold at a purity of >99%. Valid physical-chemical values are available for ADO including melting point, boiling point, vapor pressure, partition coefficient and water solubility.

Environmental releases are limited to fugitive emissions. As ADO is produced and consumed in sealed systems these releases are small.Test data indicate that ADO is stable and soluble in water. ADO's vapor pressure is very low (< 0.1 mm Hg). Therefore, it should not volatilize into the air very quickly and would tend to stay in water. No photodegradation data are available. The results of an acceptable biodegradation study indicate that ADO only slowly biodegrades in soil. No data are available on transport between environmental compartments. The high partition coefficient suggests that ADO has the potential to bioaccumulate.

Acceptable ecotoxicity data are available for rainbow trout (*Salmo gairdneri)*, bluegill sunfish (*Lepomis macrochirus)*, and the invertebrate *Daphnia magna.* Acute LC_{50}/EC_{50} values have been reported as 28 mg/L, 275 mg/L and 343 mg/L, respectively. Based on these values, ADO is considered slightly to moderately toxic to aquatic organisms. Concentrations of 500 mg/L or less of ADO have been reported to have no inhibitory effect on the metabolism of activated sludge microorganisms. No data are available on the effects of ADO on algae.

Sufficient valid mammalian information exists that indicates ADO is only slightly toxic with acute oral exposure and moderately toxic via inhalation. Three acute oral studies in rats using neat ADO report relatively consistent LD_{50s} ranging from 724 to 809 mg/kg. Administration of ADO in corn oil greatly reduces its toxicity most likely due to a reduced rate of absorption from the oil as a consequence of ADO's high solubility in oil as shown by the chemical's high partition coefficient.

Inhalation studies on aerosols of ADO determined a 4- hour LC_{50} of 1.23 mg/L and a 1-hour LC_{50} > 2 mg/L. Acute dermal data that exist indicates ADO is also slightly to moderately toxic by this route although the validity of the available studies is questionable. Toxic effects observed in adequate repeated dosing ADO diet studies of 7 days and 13-weeks were limited to depression of body weights which may have been an indirect effect of ADO as food consumption was reduced in the affected animals. Reproductive organs evaluated microscopically in the 13- week study were not affected by ADO. No data are available on ADO for developmental toxicity.

ADO was negative for mutagenicity with and without metabolic activation in two separate Ames tests. ADO was positive in a mouse lymphoma study without metabolic activation but not with metabolic activation. Data on the potential of ADO to cause chromosome aberrations is not available.

With regard to the HPV program, it is the opinion of the submitter that sufficient and acceptable information on ADO exists for: all of the required **physical-chemical properties**; for the required **environmental fate/transport**, endpoints of water stability, photodegradation, fugacity and biodegradation; for the acute fish and acute invertebrate **ecotoxicity** endpoints; and for the acute oral, acute dermal, acute inhalation, repeated dose, reproductive toxicity (based on reproductive organ evaluation in a subchronic study) and genotoxicity -point mutation **mammalian toxicity** endpoints. No additional testing needs to be performed for these endpoints.

Information for ADO on acute toxicity to algae, and mammalian developmental toxicity is lacking as a result of these studies not being available. It is the intention of the submitter to model or conduct these studies, pending EPA approval, during the calendar year 2004. While information on chromosome aberration potential is also lacking, giving consideration to the limited exposure potential and the fact that ADO was not active in either the Ames assay or mouse lymphoma assay, sponsor does not feel that this data is required. Studies will be conducted according to GLPs and reference applicable OECD guidelines. To assure that animal welfare concerns are appropriately addressed, the studies will be designed to keep animal use to a minimum to the extent possible within acceptable guidelines.

TESTING PLAN IN TABULAR FORMAT

Aldicarb Oxime **CAS no. 1646-75-9**	**Information available**	**OECD study [1]**	**GLP study**	**Other study[1]**	**Estimation Method**	**Acceptable**	**Testing Required**	**comments**
HPV Endpoint								
Physical-Chemical Properties								
Melting Point	**Y**						**N**	
Boiling Point	**Y**						**N**	
Vapor Pressure	**Y**						**N**	
Partition Coefficient	**Y**						**N**	
Water solubility	**Y**						**N**	
Environmental Fate								
Photodegradation	**N**						**N**	
Water Stability	**Y**		**Y**		**N**	**Y**	**N**	
Transport	**Y**						**N**	**Modeled**
Biodegradation	**Y**		**Y**		**N**	**Y**	**N**	
Ecotoxicity								
Acute fish	**Y**		**Y**			**Y**	**N**	
Acute invertebrate	**Y**		**Y**			**Y**	**N**	
Acute algae	**N**						**Y**	
Mammalian Toxicity								
Acute oral	**Y**		**N**			**Y**	**N**	
Acute dermal	**Y**		**N**			**Y**	**N**	
Repeated dose	**Y**		**N**			**Y**	**N**	
Genotoxicity- point mutation	**Y**		**Y**			**Y**	**N**	
Genotoxicity-chromosome aberration	**N**						**N**	**Not active in Ames and mouse lymphoma assays**
Reproductive toxicity	**Y**			**Y**		**Y**	**N**	**No effects on gonadal tissue in 90-day study**
Developmental toxicity	**N**						**Y**	

1. Most studies predate OECG Guidelines and GLPs.

For the following information sections:

*** = an asterisk prior to a subsection number indicates endpoint is a SIDS requirement**

Study reliability based on the 4-point scoring system of Klimisch *et al.* (1997) where:

1= reliable without restrictions

"studies or data…generated according to generally valid and/or internationally accepted guidelines (preferably performed according to GLP) or in which the test parameters documented are based on a specific (national) testing guideline or in which all parameters described are closely related/comparable to a guideline method"

2 = reliable with restrictions

"studies or data…(mostly not performed according to GLP), in which the test parameters documented do not totally comply with the specific testing guideline, but are sufficient to accept the data or in which investigations are described which cannot be subsumed under a testing guideline, but which are nevertheless well documented and scientifically acceptable"

3 = not reliable

"studies or data…in which there were interferences between the measuring system and the test substance or in which organisms/test systems were used which are not relevant in relation to the exposure (e.g., unphysiologic pathways of application) or which were carried out or generated according to a method which is not acceptable, the documentation of which is not sufficient for assessment and which is not convincing for an expert judgment ".

4 = not assignable

"studies or data…which do not give sufficient experimental details and which are only listed in short abstracts or secondary literature (books, reviews, etc)."

1. GENERAL INFORMATION

1.1 GENERAL SUBSTANCE INFORMATION

A.	**CAS Number**	1646-75-9
B.	**Name**	**2-Methyl-2-methylthiopropanal oxime** Aldicarb Oxime (ADO)
D..	**Molecular Formula**	$C_5H_{11}NOS$
E.	**Structural Formula**	$CH_3SC(CH_3)_2CHNOH$
F.	**Molecular Weight**	133
G.	**Type of Substance**	organic
H.	**Physical State**	clear, colorless liquid
I.	**Purity**	>99%
J.	**pH**	7

1.2	**SYNONYMS**	**Aldicarb Oxime: ADO** 2-methyl-2-methylthiopropanal oxime 2-methyl-2-(methylthio)propionaldehyde oxime 2-methyl-2-(methylthio)propionaldoxime propanal, 2-methyl-2-(methylthio)-, oxime propionaldehyde,2-methyl-2-(methylthio)-, oxime 2-(methylthio)isobutyraldehyde oxime Temik oxime
1.3	**IMPURITIES**	No significant inpurities
1.4	**ADDITIVES**	None
1.5	**QUANTITY**	1 to 5 MM lbs/yr
1.6	**USE PATTERN**	Chemical Intermediate used only at one site globally.

1.7 OCCUPATIONAL EXPOSURE LEVEL

Type: Exposure limit value established by producer, 8 hr. TWA

Value: 10 ppm (54.3 mg/m^3)

Reference: Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, Jan. 27, 2000

1.8 SOURCE OF EXPOSURE

Source: ADO is produced at only one Honeywell site, for one customer, where it is consumed as an intermediate in pesticide production. The synthesis of the product is conducted in a sealed system minimizing employee exposure

Remarks: As exposures are very low (relative to the Honeywell PEL of 10 ppm), monitoring at the production site has been conducted infrequently. The results form this monitoring confirm that exposures are low.

Date	Personal (#)	Area (#)
Aug.-Nov 1977	<0.45 ppm (8)	<0.1 ppm (16)
Feb-April 1978	≤0.29 ppm (8)	
Sept 1978	≤0.04 ppm (2)	≤0.02 ppm (5)
Oct. 1978	≤0.05 ppm (3)	≤0.12 ppm (4)
May 1985	0.05 ppm (1)	0.01 ppm (1)
Nov. 2002	<.005 to 0.012 ppm (6)	

Reference: Internal AlliedSignal (Honeywell) monitoring report dated October 12, 1995, Blake Wiseman to D. W. Stidham and results from monitoring program in November 2002.

Method: Samples are collected with personnal samplers and analyzed by HPLC.

Relialibitity: 1 Samples have been analyzed by Honeywell Industrial Hygiene staff using current technology. Procedure is described in monitoring SOP.

2. PHYSICAL-CHEMICAL DATA

*2.1 MELTING POINT

Value:	21^0C (69.8^0F)
Method:	Not specified
GLP:	Pre GLP
Remarks:	
Reliability:	2- not GLP
Reference:	Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, , Jan. 27, 2000; Arthur D. Little, Inc, Health and Safety Package for Aldicarb oxime, Feb. 21, 1989. Secondary source Beilstein-Institut zur Foerderung der Chemischen Wissenschaften (2003)

*2.2 BOILING POINT

Value:	210^0C (410^0F) @ 760 Torr 57°C (134.6°) @ 0.8 Torr
Method:	Not specified
GLP:	No predates GLPs
Remarks:	Boils with partial decomposition
Reliability:	2- not GLP
Reference:	Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, , Jan. 27, 2000; Arthur D. Little, Inc, Health and Safety Package for Aldicarb oxime, Feb. 21, 1989. Secondary source Beilstein-Institut zur Foerderung der Chemischen Wissenschaften (2003)

2.3 DENSITY (Specific gravity)

Value:	1.05 g/ml

Temperature:

Method:

GLP:

Remarks:

Reliability: 4- not assignable (insufficient method information)

Reference: Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, , Jan. 27, 2000; Arthur D. Little, Inc, Health and Safety Package for Aldicarb oxime, Feb. 21, 1989.

*2.4 VAPOR PRESSURE

Value: <0.1 mm Hg @20^{o} C
0.07616 Torr @ 25°C

Method: Calculated

GLP: Not applicable

Remarks:

Reliability: 4- not assignable (insufficient method information)

Reference: Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, , Jan. 27, 2000; Arthur D. Little, Inc, Health and Safety Package for Aldicarb oxime, Feb. 21, 1989. And Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.67 ((C) 1994-2003)

*2.5 PARTITION COEFFICIENT $\log_{10} K_{ow}$

Log Kow: 1.25

Method: calculated

GLP:	not applicable
Remarks:	Input parameters: water solubility 25000 mg/L; vapor pressure 0.1 mm Hg; BP 210°C.
Reliability:	2 Calculated value
Reference:	KOWWIN v1.67 estimate

***2.6 WATER SOLUBILITY**

Value:	2.5 wt.%
Temperature:	72^0F (22^0C)
Method:	
GLP:	
Remarks:	
Reliability:	4- not assignable (insufficient method information)
Reference:	Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, Jan. 27, 2000

2.7 Flash Point

Value:	244^oF (118^0C)
Method:	Open cup
GLP:	No
Remarks:	
Reliability:	4- not assignable (insufficient method information)
Reference:	Honeywell International Inc., Material Safety Data Sheet for Aldicarb Oxime, , Jan. 27, 2000; Arthur D. Little, Inc, Health and Safety Package for Aldicarb oxime, Feb. 21, 1989.

2.8 AUTOFLAMMABILITY

Value: 545^0F ((285^0C)

Method:

GLP:

Remarks:

Reliability: 4- not assignable (insufficient method information)

Reference: Honeywell International Inc., Material Safety Data Sheet for Aldicarb oxime, Jan. 27, 2000;

2.9 FLAMMABILITY

Results: Not flammable

Method

GLP:

Remarks:

Reference: Honeywell International Inc., Material Safety Data Sheet for Aldicarb oxime, Jan. 27, 2000;

2.10 Henry's Law Constant

Results: $7.12e^{-007}$ atm.-m^3/mole
Method: calculated from VP: 0.1 mm Hg
Water solubility: 25,000 mg/l
HENRYWIN v3.10

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

*3.1.1 PHOTODEGRADATION

No data available

*3.1.2 STABILITY IN WATER

Method:	HPLC analysis of saturated solution
Results:	Stable for at least 15 days
GLP:	Yes
Remarks:	A saturated solution of ADO was prepared by stirring excess ADO in well water for three hours and allowing it to settle for one hour. The supernatant was evaluated by maintaining the solution for 15 days and analyzing by HPLC at periodic intervals.
Reliability:	2- reliable with restrictions (test performed only at room temperature and single pH)
Reference:	Allied Chemical Corporation, (1981) *Static acute toxicity test of aldicarb oxime-Analysis of Aqueous ADO samples ,*Report No. MA-13-77-19

3.2 MONITORING DATA (ENVIRONMENTAL)

Model AopWin v1.91
Hydroxyl Radical Reaction
Overall OH Rate Constant = 4.3506 e^{-12} cm^3/molecule-sec
Half-life = 2.459 days (12-hr day; 1.5 e^6 $OH/cm^{3)}$

Soil Adsorption (PCKOCWIN v1.66)
Koc = 380.8 log Koc = 2.581

*3.3 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS (FUGACITY)

Input data:
Water solubility 25,000 mg/L
Vapor pressure: 0.1 mm Hg
Log K_{ow} = 15.1
Boiling Point: 210°C
Melting point: 21°C

Level III Fugacity Model:

	Percent	Half-life	Emissions

Air	1.92%	59 hr.	1000 kg/hr
Water	6.97%	360 hr.	1000 kg/hr
Soil	29.2%	360 hr.	1000 kg/hr
Sediment	61.9%	1.44 e^3	0

Persistence Time: 669 hr.

***3.4 BIODEGRADATION**

Method:	Static shake flask—CO_2 evolution
Test substance purity:	97.4%
Results:	Not biodegradable
GLP:	Yes
Remarks:	An acclimated mixed culture inoculum derived from activated sludge and soil was exposed to 10 mg/L organic carbon of ADO for 28 days at 23 $\pm$ 4^{0}C. Evolution of CO_2 and removal of soluble organic carbon were evaluated. Cumulative 28 day percentage CO_2 evolutions was 2.62% and cumulative 28 day soluble organic carbon removal was <1.0%
Reliability:	1- reliable without restrictions
Reference:	Allied Corporation, (1982) *Static shake flask-CO_2* evolution test of aldicarb oxime (ADO) Report No. MA-13-77-30

4. ECOTOXICOLOGY

***4.1 ACUTE TOXICITY TO FISH**

Type:	LC_{50}
Species/strain:	Bluegill sunfish (*Lepomis macrochirus)*
Exposure time:	96 hours
Value:	275 mg/L

Method:	Static acute
GLP:	Yes
Test Substance Purity:	97.4%
Remarks:	Bluegill sunfish were exposed to five nominal ADO concentrations (66, 102,158,243 and 374 mg/L) for 96 hours at 22^0C under static test conditions. The acute lethality threshold concentration at 96 hours was between 102 and 158 mg/L. A NOEL was < 66 mg/L.
Reliability:	1- reliable without restrictions
Reference:	Allied Chemical Corporation, (1981) *Static acute toxicity of aldicarb oxime (ADO) to Bluegill Sunfish, Lepsomis Macrochirus,* Report No. MA-13-77-20,

Type:	LC_{50}
Species/strain:	Rainbow trout (*Salmo gairdneri)*
Exposure time:	96 hours
Value:	28 mg/L
Method:	Static acute
GLP:	Yes
Test Substance Purity:	97.4%
Remarks:	Rainbow trout were exposed to five nominal ADO concentrations (16, 27, 44, 75 and 125 mg/L) for 96 hours at 12^0C under static test conditions. The acute lethality threshold concentration at 96 hours was between 16 and 27 mg/L. A NOEL was < 16 mg/L.
Reliability:	1- reliable without restrictions

Reference:	Allied Corporation, (1981) *Static acute toxicity of aldicarb oxime (ADO) to rainbow trout, Salmo gairdneri,* Report No. MA-13-77-23

***4.2 ACUTE TOXICITY TO AQUATIC PLANTS (algae)**

No data available, Will be conducted

***4.3 ACUTE TOXICITY TO AQUATIC INVERTEBRATES**

Type:	EC_{50}
Species/strain:	*Daphnia magna*
Exposure time:	48 hours
Value:	343 mg/L
Method:	Static acute
GLP:	Yes
Test Substance Purity:	97.4%
Remarks:	Daphnids were exposed to five nominal ADO concentrations (96,137, 196, 280 and 400 mg/L) for 48 hours under static test conditions. A NOEL was 137 mg/L
Reliability:	1- reliable without restrictions
Reference:	Allied Chemical Corporation, (1981). *The acute toxicity of aldicarb oxime (ADO) to the water flea, Daphnia magna,* Report No. MA-13-77-22.

4.4 TOXICITY TO BACTERIA

Type:	IC_{50}
Species/strain:	Activated sludge microorganisms
Exposure time:	5 hours

Value:	> 5000 mg/L
Method:	STM, ESL-009 , Microbial Toxicity (IC_{50})-Lockhart method.
GLP:	Yes
Test Substance Purity:	97.4%
Remarks:	An activated sludge inoculum was exposed to four nominal ADO concentrations (5, 50, 500 and 5000 mg/L) at 27^0C. Concentrations of ADO of 500 mg/L or less had no inhibitory effect on microbial metabolism. Approximately 20% of microbial metabolism as measured by $^{14}CO_2$ evolution was observed at 5000 mg/L. Therefore, an IC_{50} was not reached.
Reliability:	1- reliable without restrictions
Reference:	Allied Corporation, (1981), *Microbial toxicity of aldicarb oxime (ADO),* Report No. MA-13-77-24.

5. MAMMALIAN TOXICITY

5.1 ACUTE TOXICITY

*5.1.1 ACUTE ORAL TOXICITY:

Type:	LD_{50}
Species/strain:	Rats/Wistar
Exposure:	Gavage
Value:	746 mg/kg (0.71 mL/kg)
Method:	Acute intubation, nonfasted rats
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	ADO was administered to three groups of 5 male rats weighing 90-120 grams at dose levels of 2.0, 1.0 and 0.5 mL/kg. Mortality was 5/5, 3/5 and 2/5, respectively. Rats became prostrate with heavy breathing 10 minutes post dose. Deaths occurred within 30 minutes at the two highest dose levels and within 3 hours at the low dose.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, only one sex, data availability limited)
Reference:	Carnegie-Mellon Institute (1971) Miscellaneous toxicity studies, Report 34-71. Cited in: Carnegie-Mellon Institute (1974) Aldicarb Oxime: Results of Feeding in the Diet for 7 Days, Report 37-94, (conducted for Union Carbide Corporation)

Type:	LD_{50}
Species/strain:	Harlan-Wistar rats
Exposure:	Gavage
Value:	742 mg/kg (0.707 mL/kg)
Method:	Acute intubation, nonfasted rats
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	Undiluted sample of ADO designated for 7-day feeding study (see below) was tested for acute peroral intubation toxicity using nonfasted rats weighing 98-120 grams. No additional details were given in the report. Rats were reported to have unsteady gait and piloerection, were prostrate within 5 minutes, and death, when it occurred, was within 0.5 to 3 hours. Dose levels were not specified in the report.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, limited information on study design and results)
Reference:	Carnegie-Mellon Institute (1974) Aldicarb Oxime: Results of Feeding in the Diet for 7 Days, Report 37-94, (conducted for Union Carbide Corporation)

Type:	LD_{50}
Species/strain:	Rats/ Wistar
Exposure:	Gavage with undiluted ADO
Value:	809 mg/kg (0.77 mL/kg)

Method:	Acute intubation to non-fasted animals
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	Undiluted sample of ADO was administered to groups of 5 male rats weighing 90-120 grams at dose levels of 1.0 and 0. 5 mL/kg Four of five animals died at the high dose while no deaths occurred at the low dose. High dose animals were observed to be prostrate within minutes after dosing with death occurring soon after. Gross pathological examination (apparently of the animals that died) found congestion throughout the thoracic and abdominal viscera.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, only one sex, only 2 dose levels, data availability limited)
Reference:	Carnegie- Mellon Institute (1965), Range finding tests on Compound 21786, 2, methyl-2-methylthiopropionaldehyde oxime, Report no. 28-70 (conducted for Union Carbide).
Type:	LD_{50}
Species/strain:	Rats/ Harlan-Wistar
Exposure:	Gavage with ADO diluted in corn oil
Value:	2,380 mg/kg
Method:	acute intubation to non-fasted animals
GLP:	No (predates GLPs)
Test Substance:	Purity not specified

Remarks:	Male rats (number not specified) weighing 90-120 grams were dosed by gavage with ADO in corn oil. LD_{50} calculated by the moving average method is reported. Higher LD_{50} than reported for undiluted ADO likely due to reduced absorption from the oil vehicle related to high solubility in oil as shown by partition coefficient for ADO.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, limited information on study design and results)
Reference:	Carnegie-Mellon Institute, (1970), TEMIK and other materials, Miscellaneous single dose peroral and parenteral LD_{50} assays and some joint action studies, Report no. 37-94 (conducted for Union Carbide).

5.1.2 ACUTE INHALATION TOXICITY:

Type:	LC_{50}
Species/strain:	Crl:CD (SD) BR rats
Exposure:	4- hour
Value:	1,230 mg/m^3 *
Method:	Acute, whole body aerosol inhalation
GLP:	Yes
Test Substance:	Purity not specified
Remarks:	Four groups of 5 male and 5 female rats received whole-body inhalation exposures to aerosol atmospheres of ADO having a mass median diameter of 2.85 micrometers and geometric standard deviation of 1.93. Gravimetric time-weighted average concentrations were 0.67, 1.12, 2.55 and 4.91 mg/L. The animals were followed for 14 days following the exposure. Mortality occurred at all

exposure levels tested. Females were slightly more sensitive than males. Major clinical signs included prostration, ataxia, tremors, irregular breathing, salivation and lacrimation. Animals dying exhibited gross abnormalities primarily of the lungs (red discoloration).

*Exposures of the high and low exposure groups were for 3.5 hours rather than 4 hours due to insufficient test material. Study director recalculated original LC_{50} of 1,560 mg/m^3 assuming 2 and 1 additional deaths would have occurred in the high and low exposure groups , respectively, with an additional 30 min. of exposure.

Reliability: 2- reliable with restrictions (< 4hour exposures at low and high dose requiring adjustment of LC_{50})

Reference: Toxigenics, Inc, (1984), Four Hour Acute Aerosol Inhalation Toxicity Study in Rats of Aldicarb Oxime. Report 420-1434 (conducted for Union Carbide Corporation).

Type: Inhalation-limit test

Species/strain: Rats / Sherman-Wistar

Exposure: 1- hour

Value: >2 mg/L

Method: Acute, whole body inhalation. Performed according to criteria specified in Paragraph 191.1 (c) (2) and (f) (2) of the Final Order, Enforcement Regulations, Federal Register, vol 26, no 155, p. 7336, 12 August, 1961).

GLP: No (predates GLPs)

Test Substance: Purity not specified

Remarks: Ten rats (sex not specified) with an average weight of 285 grams were exposed to ADO for

	one hour in a 72 liter glass chamber. Air flow was 10 L/min. ADO was generated as a fine aerosol. Nominal concentration was 2 mg/L. No deaths occurred. Animals appeared docile and stressed immediately after the exposure with full recovery in 24 hours. No other information given in this one page report.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, limited data presented in report, only nominal exposure concentration)
Reference:	Food and Drug Research Laboratories, (1974). Acute inhalation study of ADO #50-4535-49C, (conducted for Allied Chemical Inc.).
Type:	Inhalation- limit test
Species/strain:	Rats/ Wistar
Exposure:	8 hour whole body exposure
Value:	No deaths at saturated vapor
Method:	Static exposure. Saturated vapor was generated by spreading 50 grams of chemical over 200 cm^2 area on a shallow tray placed near the top of a 120-liter glass chamber which was subsequently sealed for at least 16 hours with intermittent agitation with a fan. Rats were introduced into the chamber in a gasketed drawer-type cage designed and operated to minimize vapor loss. (method described in earlier report from this lab, assumed method was unchanged for this study).
GLP:	No (predates GLPs)
Test Substance:	Purity (2 samples: 92.7% and 99.25%)
Remarks:	Each of the two samples ADO were tested separately. In each study, 6 animals were

exposed to the saturated vapor for 8 hours. The ADO sample of 92.7% purity caused no mortality but produced the following signs of toxicity: Eyes closed within 30 minutes, lacrimation within 60 minutes, slight coordination loss within 90 minutes. Signs were no longer present after 4 hours of the 8 hour exposure. The ADO sample of 99.25% purity caused no deaths but produced signs of closed eyes within 30 minutes, slight gasping within 60 minutes, slight coordination loss within 90 minutes. Signs were no longer present after 4 hours of the 8 hour exposure. The report concludes that the signs of toxicity observed may have been due to the presence of impurities that gradually reduced in concentration either through loss or chemical reactions during the course of the exposure.

Reliability: 3-not reliable (method is questionable, no determination of exposure level, possibility of leaks and/or impurities stated)

Reference: Carnegie-Mellon Institute (1976), Miscellaneous toxicity studies, Report no. 37-94 (conducted for Union Carbide).

*5.1.3 ACUTE DERMAL TOXICITY

Type: LD_{50}

Species/strain: albino rabbit

Exposure: 24 hours, Intact skin

Value: 1900 mg/kg

Method: 16 CFR 1500.40

GLP: No (predates GLPs)

Test Substance: Purity not specified

Remarks:	Groups of 5 rabbits (sex not specified) were exposed dermally to ADO at doses of 0.02, 0.2, 0.43, 0.928 and 2.0 g/kg. Mortality occurred in all groups except at 0.928 mg/kg. The dose response was “U-shaped” (2/5, 1/5, 1/5, 0/5 and 3/5, respectively). No gross pathological effects were observed at necropsy. No additional information is provided in the single page report.
Reliability:	2 limited study detail and shape of the dose response questions the reliability of this study
Reference:	Food and Drug Research Laboratories, Inc., 1975), Acute dermal toxicity study in rabbits, (conducted for Allied Chemical Corporation)
Type:	Lethality
Species/strain:	Albino rabbit/ New Zealand
Exposure:	24 hours under occluded conditions
Value:	210 mg/kg (0.2 mL/kg)
Method:	Exposure to undiluted ADO “standard “ conditions. Exposure under VINYLITE covering.
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	Four male rabbits were exposed dermally to ADO at a dose of 0.2 mL/kg. Mortality occurred in one of the rabbits. No signs or symptoms were reported. Necropsy was not performed on the dead rabbit because of autolysis. Mortality pattern consistent with previous study.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, limited

	information on study design and results, only one dose level tested)
Reference:	Carnegie-Mellon Institute (1965), Range finding tests on Compound 21786, 2, methyl-2-methylthiopropionaldehyde oxime, Report no. 28-70 (conducted for Union Carbide).

5.1.4 ACUTE TOXICITY-OTHER ROUTES

Type:	LD_{50}
Species/strain:	Mouse (albino)
Exposure:	Intraperitoneal
Value:	< 100 mg/kg
Method:	Single dose range finding study
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	5 male mice weighing 24 to 28 grams were injected with ADO as a 1% aqueous solution. All of the animals died within 24 hours of the injection. Reported signs included marked depression and gasping. Eye and pinna reflexes appeared normal.
Reliability:	3-not reliable (irrelevant route of exposure, single dose)
Reference:	Carnegie-Mellon Institute (1965), Range finding tests on Compound 21786, 2, methyl-2-methylthiopropionaldehyde oxime, Report no. 28-70 (conducted for Union Carbide).

5.2 CORROSIVENESS/IRRITATION:

Type:	Skin irritation
Species/strain:	Rabbit
Exposure:	Unknown
Value:	moderate irritant
Method:	ADO (0.01mL) applied undiluted to the clipped. Intact skin of the belly of 5 rabbit. Exposure was not occluded (uncovered).
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	ADO produced moderate erythema on 3 animals and moderate to marked capillary injection on 2 others. Test scored as grade 4 based on a ten point system.
Reliability:	2- reliable with restrictions (method different from currently acceptable method, scoring system is not classic Draize yet provides some usable information on skin irritation potential)
Reference:	Carnegie-Mellon Institute (1965), Range finding tests on Compound 21786, 2, methyl-2-methylthiopropionaldehyde oxime, Report no. 28-70 (conducted for Union Carbide).

Type:	Eye irritation
Species/strain:	Rabbit
Exposure:	0.005 mL undiluted ADO or 0.5 mL of a 15% or 5% solution of ADO in propylene glycol.
Value:	Corrosive/severe

Method:	Single exposure. ADO introduced into conjunctival sac. Observed one hour and 24 hours after exposure. Total number of animals used not specified.
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	Undiluted ADO (0.005 mL) or 0.5 mL of a 15% ADO in propylene glycol caused moderately severe corneal necrosis. 5% ADO caused no injury in 2 eyes and only a trace of diffuse corneal necrosis in a third. Some eyelid irritation was also noted. Test scored as grade 8 based on a ten point system.
Reliability:	2- reliable with restrictions (method different from currently acceptable method, scoring system is not classic Draize yet provides useful information on skin irritation potential)
Reference:	Carnegie-Mellon Institute (1965), Range finding tests on Compound 21786, 2, methyl-2-methylthiopropionaldehyde oxime, Report no. 28-70 (conducted for Union Carbide).

5.3 SKIN SENSITIZATION:

No data available

***5.4 REPEATED DOSE TOXICITY**

Type:	Subchronic
Species/strain:	Crl:CD (SD) rats albino rats
Method:	ADO incorporated into diet
Route of Administration:	Oral, through diet

Exposure Period:	13 weeks continuous
Dose:	Target dose: 125, 25 , 5 mg/kg Attained dose: 118.5, 23.8, 4.8 mg/kg (males) 120.2, 24.3, 4.8 mg/kg (females)
Control Group:	Yes, feed without test material
NOEL:	120.2 mg/kg*
LOEL:	> 120.2 mg/kg* *assuming observed depression of body weights in females at this dose level was a result of reduced food consumption and not a direct toxic effect of ADO.
Results:	Twenty five rats per sex per group were administered ADO for thirteen weeks in feed at target levels of 5, 25, and 125 mg/kg. No mortality occurred in the study. ADO caused a depression in body weight gain in high-dose females from weeks 3 through 13 of the study. This was associated with a decrease in food consumption. No other signs of toxicity including mortality, clinical signs, changes in hematology or organ weights or gross or microscopic pathology were associated with ADO administration..
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	Well designed and reported study. Criteria evaluated included clinical signs, mortality, body weight, food consumption, hematology and clinical chemistries, organ weights (including testes) and gross and microscopic pathology (including testes and ovaries). Parameters of toxicity evaluated were consistent with or exceed current practices (e.g., hematology and clinical chemistries performed on weeks 4, 8, and 13)

Reliability:	1- reliable without restrictions
Reference:	Hazleton Laboratories, Inc (1976), 13-Week Toxicity Study in Rats, Report 165-168 (conducted for Allied Chemical Corporation
Type:	Subacute
Species/strain:	Harlan-Wistar albino rats
Method:	ADO incorporated into diet
Route of Administration:	Oral, through diet
Exposure Period:	7 days continuous
Dose:	Target dose: 1,000, 500, 250 mg/kg (study #1) 125, 62.5, 31.25 (study #2) Attained dose: 728, 409, 243, 121, 57.9 and 27.6 mg/kg
Control Group:	Yes, feed without test material
NOEL:	27.6 mg/kg
LOEL:	57.9 mg/kg
Results:	Five rats per group per sex were administered ADO in diet at daily target doses ranging from 31.25 to 1000 mg/kg for 7 days. Lower body weight gains than controls at dose levels at or above 57.9 mg/kg for males and 121 mg/kg for females were observed. The degree of the effect on body weight gains was dose-related, being only slight and transient at the lower dose levels. Food consumption was reduced at the higher dose levels. No deaths occurred. Weights (relative to body weight) of the liver and kidneys were not significantly affected.
GLP:	No (predates GLPs)
Test Substance:	Purity not specified

Remarks:	The report describes two separate studies. The initial study was conducted at the higher dose levels followed by a second study at lower dose levels. Parameters examined included mortality, food consumption, bodyweights, and liver and kidney weights. Study report consists of only 5 pages. No protocol available. Limited endpoints of toxicity evaluated.
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, Limited endpoints of toxicity evaluated, no histopathology)
Reference:	Carnegie-Mellon Institute, (1974), Aldicarb Oxime: Results of Feeding in the Diet for 7 Days ,Report 37-94, (conducted for Union Carbide Corporation)

5.5 GENETIC TOXICITY *IN VITRO*

*5.5.1 GENE MUTATION:

Type:	Ames test
Test System:	*Salmonella typhimurium* Strains TA98, TA100, TA1535, TA1537 and TA1538
Test substance:	Purity not specified
Concentration:	100, 333, 1,000, 3,333, and 10,000 μg/plate
Metabolic activation:	With and without Arochlor- induced rat (F-344) and hamster (Syrian golden) S-9
Method:	Plate incorporation, included solvent (DMSO) and positive controls. Tested in triplicate. Doses selected from range finding study.
GLP:	Yes
Results:	Not mutagenic with or without metabolic activation.
Remarks:	Conducted for the National Toxicology Program (NTP).
Reliability:	1- reliable without restrictions
Reference:	Rogers-Back, A.M., Lawlor, T.E., Cameron, T.P. and V.C. Dunkel, (1988), Genotoxicity of 6 oxime compounds in Salmonella/mammalian-microsome assay and mouse lymphoma $TK^{+/-}$ assay. *Mutation Research* 204: 149-162,.

Type:	Ames test
Test System:	*Salmonella typhimurium* Strains TA98, TA100, TA1535 and TA1538
Test substance:	Purity not specified

Concentration:	5, 10, 50, 100, 500, 1,000 and 5,000 µg/plate
Metabolic activation:	With and without rat Arochlor- induced S-9.
Method:	Plate incorporation
GLP:	No (predates GLPs)
Results:	Not mutagenic with or without metabolic activation. ADO was slightly cytotoxic at 5,000 µg.
Remarks:	No replicate performed. Concurrent positive control was reported.
Reliability:	2- reliable with restrictions (Predates GLPs)
Reference:	Stanford Research Institute (SRI), (1975), Microbial mutagenesis assays of Allied Chemical Corporation compounds, report LSC-4192. (conducted for Allied Chemical Corporation)
Type:	Mouse lymphoma
Test System:	L5178Y $tk^{+/-}$ 3.7.2C mouse lymphoma cells
Test substance:	Purity not specified
Concentration:	1.1, 1.2, 1.3, 1.4, 1.5,and 1.6 µL/mL
Metabolic activation:	With and without Arochlor- induced rat (F-344) S-9
Method:	Method of Clive and Spector. Doses selected from range finding study. Solvent and positive controls utilized. Study run in duplicate.
GLP:	Yes

Results:	Equivocal result without metabolic activation. A greater than 2-fold increase in mutant frequency was noted only at the highest dose of 1.6 µL/mL which produced only 11% total growth. There was no clear dose-response with the curve being relatively flat. ADO was not mutagenic with metabolic activation.
Remarks:	Conducted for the National Toxicology Program (NTP).
Reliability:	1- reliable without restrictions
Reference:	Rogers-Back, A.M., Lawlor, T.E., Cameron, T.P. and V.C. Dunkel, (1988), Genotoxicity of 6 oxime compounds in Salmonella/mammalian-microsome assay and mouse lymphoma $TK^{+/-}$ assay. *Mutation Research* 204: 149-162,.

***5.5.2 CHROMOSOME ABERRATIONS:**

No data available

5.6 GENETIC TOXICITY *IN VIVO*:

No data available

5.7 CARCINOGENICITY:

No data available

***5.8 TOXICITY TO REPRODUCTION:**

Type:	Subchronic
Species/strain:	Crl:CD (SD) rats albino rats
Method:	ADO incorporated into diet
Route of Administration:	Oral, through diet
Exposure Period:	13 weeks continuous

Dose:	Target dose: 125, 25 , 5 mg/kg Attained dose: 118.5, 23.8, 4.8 mg/kg (males) 120.2, 24.3, 4.8 mg/kg (females)
Control Group:	Yes, feed without test material
Results:	Twenty five rats per sex per group were administered ADO for thirteen weeks in feed at target levels of 5, 25, and 125 mg/kg. No changes in testicular weight or microscopic pathology of the testes or ovaries were observed.
GLP:	No (predates GLPs)
Test Substance:	Purity not specified
Remarks:	Well designed subchronic study. Criteria evaluated included testes weight and gross and microscopic pathology of the testes and ovaries).
Reliability:	2- reliable with restrictions (predated GLPs but conducted at credible laboratory, not designed as a reproduction study but incorporates evaluation of reproductive organs)
Reference:	Hazleton Laboratories, Inc (1976), 13-Week Toxicity Study in Rats, Report 165-168 (conducted for Allied Chemical Corporation)

*5.9 DEVELPOMENTAL TOXICITY/TERATOGENICITY:

No data available.
Will be conducted

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Note:
The laboratory referenced here as Carnegie-Mellon Institute was the Chemical Hygiene Fellowship of Carnegie-Mellon University, Pittsburgh, PA. identified on the various reports as Carnegie-Mellon Institute of Research or Mellon Institute.

Allied Chemical Corporation has changed names over the years. These names include Allied Corporation, AlliedSignal Corporation and most recently, Honeywell International Inc.